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(54) Title: FORMULATION FOR NASAL INSULIN DELIVERY

(57) Abstract

The invention is related to a pharmaceutical preparation for nasal insulin administration in men comprising the polypeptide hormone insulin, or an analogue thereof, and a methylated β-cyclodextrin having a degree of substitution between 0.5 and 3.0, and being a solid (powder) or a semi solid preparation. The preparation can be produced by performing a process comprising the steps of (1) producing a solution of at least the polypeptide hormone insulin, or an analogue thereof, and a methylated cyclodextrin, (2) freezing the said solution, and (3) lyophilizing the frozen substance.

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FORMULATION FOR NASAL INSULIN DELIVERY.

The invention is related to a pharmaceutical preparation of a form and composition suitable for nasal administration of insulin, or an analogue thereof, and to a process of preparing such preparation.

Insulin is a polypeptide hormone of 51 amino acids. It is synthesized in the pancreas and it functions as a physiological regulator of the carbohydrate metabolism in the body. For many years insulin has been therapeutically used in patients with diabetes mellitus, to lower increased blood sugar levels in these patients. Oral administration of insulin is not feasible because of its peptide structure, since it is broken down in the gastro-intestinal tract. Therefore, it is usual to administer the drug by parenteral injections, for example subcutaneously or intramuscularly. However, these invasive methods of administration are associated with delayed and irregular absorption from the site of injection, probably due to hexamer formation. Moreover, daily injection therapy causes the patients considerable inconvenience: injections are experienced as painful and traumatic, are irreversible, and the patient must learn the injection technique.

For many years already industry and research centers are intensively investigating and testing non-invasive routes for the administration of insulin, in particular the nasal route of administration. Publications - such as patents and patent applications - show such developments and make clear that there is an urgent need for a successful technique of nasal administration of insulin. Advantages of nasal administration: the nasal cavity is easily accessible for drug administration; the nasal epithelial tissue has a rich vasculature; the nasal route avoids degradation of the drug in the gastro-intestinal tract, and the nasal route is eminently suitable for self-medication. Furthermore,

intranasal insulin administration would not only circumvent the procedure of injection, but will probably also result in more predictable blood levels.

In principle, intranasal administration of insulin leads to poor bioavailability since insulin is a high molecular weight and hydrophilic substance and, therefore, is hardly capable of passing the lipophilic nasal epithelial barrier. However, the nasal bioavailability can be improved by using so-called absorption enhancing adjuvants.

In the literature many absorption enhancers have been described for nasal administration of insulin, including ionic and non-ionic surfactants such as bile salts (Gordon et al., Proc. Natl. Acad. Sci. U.S.A. 82 (1985) 7419-7421; EP-A-0 111 841) and polyoxyethylene alcohol ethers (Hirai et al., Int. J. Pharm. 9 (1981) 165-172; GB-A-1 527 605), fatty acids and phospholipids (Mishima et al., J. Pharmacobio-Dyn. 10 (1987) 624-631; Illum et al., Int. J. Pharm. 57 (1989) 49-54; PCT/DK-87.00158), chelating agents such as EDTA (US-A-4 476 116), and fusidate derivatives such as STDHF (Longenecker et al., J. Pharm. Sci. 76 (1987) 351-355; Deurloo et al., Pharm. Res. 6 (1989) 853-856; Kissel et al., Pharm. Res. 9 (1992) 52-57; US-A-4 548 922).

As described in these publications all the said absorption enhancers resulted in an increased bioavailability of nasally administered insulin, but the reproducibility of the resulting insulin absorption profiles in the blood leaves to be desired. Moreover, many of these absorption enhancers are harmful to the nasal epithelial membranes (Wheatley et al., J. Controlled Rel. 8 (1988) 167-177; Ennis et al., Pharm. Res. 7 (1990) 468-475; Chandler et al., Int. J. Pharm. 76 (1991) 61-70), and various of these substances may seriously inhibit the natural movement of the cilia in the nose (Hermens et al., Pharm. Res. 7 (1990)

144-146; Merkus et al., J. Controlled Rel. 24 (1993), 201-208). So far, the insulin absorption enhancers used, like bile acids and phospholipids have yi lded results and side effects which were prohibitive for further development.

Also cyclodextrins have been shown to be a class of absorption enhancers for nasal drug delivery. These compounds are cyclic oligosaccharides of 6, 7 or 8 glucose units, named α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), and γ-cyclodextrin (γ-CD) respectively. The inside of these cyclic molecules has lipophilic characteristics, whereas the outside is hydrophilic. Because of these properties, cyclodextrins are able to form inclusion complexes with lipophilic drugs, thereby increasing their water-solubility (Uekama et al., Int. J. Pharm. 10 (1982) 1-15).

The application of various compounds, including cyclodextrins, for nasal administration of insulin is extensively investigated and tested by NOVO Industri (EP-A-0 308 181). This publication mentions all kinds and derivatives of monosaccharides and oligosaccharides, including α-, β-, γ-cyclodextrins and derivatives thereof. It also mentions that the preparation may be solid, a powder (for snuffing) or liquid (administration as spray). Tests in rabbits appeared to be promising. However, no positive results with administration in men came out of this development and the said patent application is lapsed.

According to WO-92/16196 it is proposed by NOVO to increase the absorption of polypeptide pharmaceuticals, including insulin, by using a powder preparation containing three different constituents, namely:

(a) a lower alkylether of cellulose, preferably hydroxypropylmethylcellulose or methylcellulose,
(b) a cyclodextrin, preferably α-cyclodextrin, and
(c) a phospholipid, preferably didecanoyl-L-α-phosphatidylcholine.

Thus, WO-92/16196 teaches that one needs as absorption enhancers didecanoyl-L-α-phosphatidylcholine as well as α-cyclodextrin and an alkylether of cellulose.

Earlier investigations and tests by applicant were related to nasal formulations of estradiol and progesterone containing dimethyl-β-cyclodextrin as solubilizer and enhancer. These formulations appeared to substantially increase the bioavailability of these steroid hormones in rabbits, rats and men. Thereby the preparation is administered as a spray in the nasal cavity (Hermens et al., Pharm. Res. 7 (1990) 500-503; Schipper et al., Int. J. Pharm. 64 (1990) 61-66; Hermens et al., Eur. J. Obstet. Gynecol. Reprod. Biol. 40 (1991) 35-41; Hermens et al., Eur. J. Obstet. Gynecol. Reprod. Biol. 43 (1992) 65-70; EPA-0 349 091).

Based on that, investigations and tests have been performed with nasal insulin administration using dimethyl-β-cyclodextrin as enhancer. The preparation was brought in a liquid form as a spray in the nasal cavity. Promising results has been achieved in rats (Merkus et al., Pharm. Res. 8 (1991) 588-592; Schipper et al., J. Controlled Rel. 21 (1992) 173-186; NL-A-90.01681; WO-92/01440). However, tests in men did not have positive results.

After all the above experiences, it was surprising that a specific derivative only in a specific condition turned out to have very good results with administration in men.

According to the invention a pharmaceutical preparation for nasal insulin administration in men is a solid (powder) or semi solid preparation comprising at least the polypeptide hormone insuline, or an analogue thereof, as an active agent, and a methylated β-cyclodextrin (methyl-β-cyclodextrin) having a degree of substitution (D.S.) between 0.5 and 3.0, preferably between 1.4 and 2.4, more preferably

approximately 1.8 as an absorption enhancing agent.

After the negative results when testing this c mposition in men with nasal administration as a liquid spray, it was not obvious whatsoever to test exactly the same composition in a solid condition. There is no publication showing that a different result was to be expected.

The nasal formulation according to the invention will in practice contain a pharmacologically active amount of insulin, or an analogue thereof, as the active agent present therein.

It is found that insulin is absorbed faster after nasal administration when the capacity of self-association of the insulin molecule is reduced. Several insulin analogues show a significantly reduced self-association, for instance products made by DNA techniques, like the insulin analogue Asp (B10), insulin analogue Asp (B 28), insulin analogue Asp (B 29) and insulin analogue Glu (B 27). Also insulin analogue Lys (B 28)-Pro (B 29) is a good candidate for intranasal administration according to this invention, because it shows a reduced self-association and a short duration of action. (M.A.J.M. Jacobs and R.J. Heine, Insulin analogues: New horizons or false dawns, Diabetes Reviews, Vol 2, No 4, Oct. 1993, 2-4).

Furthermore it was found that an excellent absorption can be obtained in case the insulin molecules are administered substantially as insulin monomers. Accordingly it turned out that the lyophilization and any further treatment of the powder should be performed in such a way that no final residual moisture will remain present. Such moisture may induce aggregation of the insulin molecules into insulin dimers, hexamers and/or octamers, resulting in less effective nasal insulin absorption. Also the presence of cyclodextrin in the powder formulation according to the

invention reduces the association of insulin molecules.

Preparations in the form of a powder formulation suitable for nasal administration may for instance contain 2 to 200 IU of the active agent per nasal dose. As regards the amount of methyl-β-cyclodextrin, the powder preparation will contain an amount thereof that enhances the absorption of the active agent present. Methyl-β-cyclodextrin amounts of 0.3 to 30 μmoles per dose are options, although amounts of 0.75 to 15 μmoles per dose are preferable.

The nasal preparations according to the invention may also contain one or more adjuvants conventionally used in nasal drug formulations, such as preservatives, stabilizers, excipients (e.g. lactose, maltose, cellulose, mannitol, sorbitol), pH-controlling compounds and complexing agents etc. Agents suitable for these and other purposes are known in the pharmaceutical literature and to men skilled in the art of nasal drug delivery.

Furthermore, according to the invention, a process for preparing a solid or semi solid pharmaceutical preparation comprises at least the following steps: (1) producing a solution of at least the polypeptide hormone insulin, or an analogue thereof, and a methylated cyclodextrin having a degree of substitution between 0.5 and 3.0, preferably between 1.4 and 2.4, more preferably approx. 1.8, (2) freezing the said solution, and (3) lyophilizing the frozen substance.

The invention also relates to a dispenser for nasal administration containing a preparation according to the invention.

The invention will now be illustrated in and by the following examples.

Experiments

Experiments have been performed involving four healthy male volunteers with the age of 26 to 51 years (body weight ranging 70-85 kg) after obtaining their informed consent. Preparations of insulin/methyl-β-cyclodextrin has been nasally administered in all four persons: as a liquid preparation (spray) in two persons and as a solid preparation (powder) in the other two persons.
The absorption of nasally administered insulin can both be judged from the plasma insulin concentration profile and the blood glucose lowering action of insulin. Thereby, plasma C-peptide concentrations reflect suppression of endogenous pancreatic insulin secretion.

Every 5 minutes from 10 minutes before to 60-120 minutes after nasal instillation of the insulin/methyl-β-cyclodextrin formulations, venous blood samples of approx. 5 ml were taken using Venoject evacuated blood collecting tubes. A part of these blood samples was used directly for assaying the glucose concentrations by means of Haemoglucotest strips in combination with a Reflolux reflectance meter. Then the blood samples were processed into plasma by means of centrifugation. Finally, the plasma insulin and C-peptide concentrations were determined with commercially available radioimmunoassay kits specific for human insulin and C-peptide, respectively.

The results of the nasal administration of insulin/methylβ-cyclodextrin preparations will be discussed referring to the drawing:
Fig. 1 shows three diagrams (A, B and C) reflecting the results of liquid administration in two persons, and
Fig. 2 shows three diagrams (A, B and C) reflecting the results of solid (powder) administration in two persons.

Diagrams A show plasma insulin concentrations in mIU/l; diagrams B show blood glucose concentrations in mmol/l, and diagrams C show plasma C-peptide concentrations in nmol/l, all during the indicated period.

(1) Preparation of nasal insulin formulations.

Liquid nasal insulin preparations were prepared by dissolving human insulin powder (26 IU/mg) in physiological saline solutions containing 2.5 mM HCl. The solutions were neutralized with 0.1 M NaOH. Final insulin concentration was 17.2 mg/ml. For nasal administration methyl-β-cyclodextrin was added to the insulin solution, resulting in the following two liquid insulin/methyl-β-cyclodextrin formulations:

- 17.2 mg/ml insulin with 5% (w/v) methyl-β-cyclodextrin, and
- 17.2 mg/ml insulin with 20% (w/v) methyl-β-cyclodextrin.

Solid (powder) insulin preparations were prepared by dissolving human insulin powder in 2.5 mM HCl to a concentration of 14.5 mg/ml. Methyl-β-cyclodextrin was subsequently added to a molar concentration of 75 mM (9.5% w/v). The insulin solutions were then frozen in liquid nitrogen and lyophilized at a pressure of about 0.01 mm Hg at least 16 hrs in a freeze dryer Modulyo (Edwards).

The liquid and solid preparations were stored at 4°C until use. The amount of insulin in all formulations was checked prior to the experiments with reversed-phase HPLC analysis.

(2) Nasal administration of the liquid and powder preparations.

The volunteers had an overnight fast. Two intravenous lines were put up, one in each arm: one for withdrawal of blood samples, the other for possible 10% (w/v) glucose administration.

Liquid insulin/methyl-β-cyclodextrin preparations were administered as a spray with a commercially available metered dose pump with a stated volume of delivery of 0.09 ml (1 puff = 0.09 ml x 26 IU insulin/mg x 17.2 mg/ml = 40 IU insulin). The delivery was as follows:

- Person 1 (indicated in the drawing with □):
  insulin dose 40 IU (20 IU per nostril) with 5% (3.75 μmoles per nostril) methyl-β-cyclodextrin.
- Person 2 (indicated in the drawing with ■):
  insulin dose 80 IU (40 IU per nostril) with 20% (15 μmoles per nostril) methyl-β-cyclodextrin.

Solid (powder) insulin/methyl-β-cyclodextrin preparations were administered by inhalation through the nose. The delivery was as follows:

- Person 3 (indicated in the drawing with ○):
  insulin dose 40 IU (20 IU per nostril) with 7.5 μmoles methyl-β-cyclodextrin (3.75 μmoles per nostril).

- Person 4 (indicated in the drawing with ●):
  insulin dose 80 IU (40 IU per nostril) with 15 μmoles methyl-β-cyclodextrin (7.5 μmoles per nostril).

(3) Results of the administrations.

As will be clear from fig. 1, none of the two liquid insulin/methyl-β-cyclodextrin formulations (person 1 and person 2) resulted in significant changes of plasma insulin (diagram A) and C-peptid (diagram C) levels. Also blo d

glucose concentrations (diagram B) were not different from their initial values (i.e. concentrations measured just before administration of the insulin/methyl-β-cyclodextrin solutions).

In contrast to the liquid preparations, nasal administration of the solid (powder) formulation appeared to be very effective. As shown in fig. 2 nasal instillation of the powder formulation resulted in remarkable increased plasma insulin levels.

In person 3 the peak plasma concentration was 48 mIU/l. This peak concentration was already reached after 20 minutes, which indicates that the insulin powder was quickly absorbed. The insulin concentrations returned to endogenous levels after about 80 minutes. A decrease in blood glucose of 30% to a minimum of 3.2 mmol/l was observed, and after the 2 hours of the experiment the glucose concentrations were still reduced. Moreover, plasma C-peptide levels were decreased.

Administration of the powder formulation in the 2-fold higher insulin dose (person 4, 80 IU) resulted in even higher insulin absorption leading to a peak insulin concentration of 67 mIU/l, already 15 minutes after administration. Because of this large insulin absorption the plasma glucose levels decreased very rapidly and extensively. Therefore, as indicated in the diagrams of fig. 2 with arrows, glucose substitution was given by infusion to the volunteer three times. The additional glucose administration is also reflected by the peak observed in the plasma C-peptide concentrations (diagram C). The insulin and glucose levels returned to normal values after 80 and 120 minutes respectively.

It is very surprising that, in contrast to the expectation, after the investigations and t sts with liquid nasal

insulin/methyl-β-cyclodextrin preparations, these studies and experiments in human volunteers indicate clearly that the preparations in solid (powder) formulation result not only in a significant increased absorption but also in a surprising high absorption of insulin.

No side effects were reported. To further verify the very positive results of the experiments a large trial has been performed, using the insulin/methyl-ß-cyclodextrin powder formulation in 6 healthy volunteers and in 6 diabetes mellitus patients. The lyophilized powder formulation was prepared according to (1) above.

For the intranasal insulin administration individual dosages of insulin-methyl ß-cyclodextrin powder were prepared, containing 1.2 IU insulin/kg body weight, divided in two doses (one dose per nostril). After nasal inhalation of the powder formulation, the insulin levels started to rise immediately. In the 6 volunteers, insulin peak levels were reached after about 15 minutes, returning to baseline 90 minutes after administration. The action profile of the absorbed insulin was determined by the glucose infusion rate according to the euglycemic clamp technique. The glucose infusion rate in the 6 volunteers showed also an immediate rise, with a peak after about 30 minutes and a slowly decreasing level up to 90 minutes. The glucose infusion could be discontinued after 120 minutes.

In the 6 diabetic patients a similar insulin absorption was found. An immediate rise of the insulin levels, with a peak level at 5 to 10 minutes after administration, followed by a slow decrease from 10 to 120 minutes. The glucose infusion rate, as a measure of the insulin action, started to increase immediately, with a plateau from 20 to 40 minutes followed by a decrease to 90 minutes.

The side effects of intranasally administered insulin methyl ß-cyclodextrin powder in the 6 healthy volunteers and the 6 Diabetes Mellitus patients were recorded during and immediately after the clamp as follows:

Score:	0	1	2	3	4	5	sneezing
Volunteers:		4	2				1
DM patients:		5	1				

Whereby the score categories were:

0 = no effect
1 = initial intranasal itch
2 = light itch
3 = irritation and nasal discharge
4 = irritation, nasal discharge and tears
5 = painful irritation, discharge, tears and bleeding
(Any tendency to sneeze was recorded)

As will be clear from the above registration, the side effects of the intranasal administration according to the invention are very low.

Also from this study, it appears that the intranasal administration of an insulin-methyl ß-cyclodextrin powder leads to a clinically effective insulin absorption and action. The insulin pharmacokinetic profile after nasal administration closely mimics the physiological postprandial insulin profile in nondiabetics, being a considerable advantage of this nasal insulin formulation.

In addition, other species or other relative concentrations of insulin and cyclodextrins in the powder formulation are options to optimize the formulation.

During 70 years diabetes patients had only one possibility to survive: insuline administration by parenteral injection, and many people had looked for alternative methods of administration. After that, the actual invention will be of great importance for many diabetes patients.

Claims:

1. A pharmaceutical preparation for nasal insulin administration in men comprising the polypeptide hormone insulin, or an analogue thereof, and a methylated β-cyclodextrin having a degree of substitution between 0.5 and 3.0, and being a solid (powder) or semi solid preparation.

2. A pharmaceutical preparation according to claim 1, characterized in that the degree of substitution is between 1.4 and 2.4.

3. A pharmaceutical preparation according to any of the preceding claims, characterized in that the insulin is substantially present as insulin monomers.

4. A pharmaceutical preparation according to any of the preceding claims, characterized in that the preparation contains an insulin analogue having a reduced capacity of self-association.

5. Process for preparing a solid or semi solid pharmaceutical preparation for nasal administration in men of insulin, or an analogue thereof, comprising the steps of (1) producing a solution of at least the polypeptidehormone insulin, or an analogue thereof, and a methylated cyclodextrin having a degree of substitution between 0.5 and 3.0, (2) freezing the said solution, and (3) lyophilizing the frozen substance.

6. Process according to claim 5, characterized in that the degree of substitution is between 1.4 and 2.4.

7. Process according to claim 5 or 6, characterized in that the lyophilizing is perform d by using a procedure by which residual moisture is avoided.

8. Device comprising a dispenser for nasal administration containing a certain quantity of the pharmaceutical preparation according to one of the claims 1-4.

9. Method of treating diabetes by administering a pharmaceutical composition according to one of the claims 1-4 to the nasal mucosa.

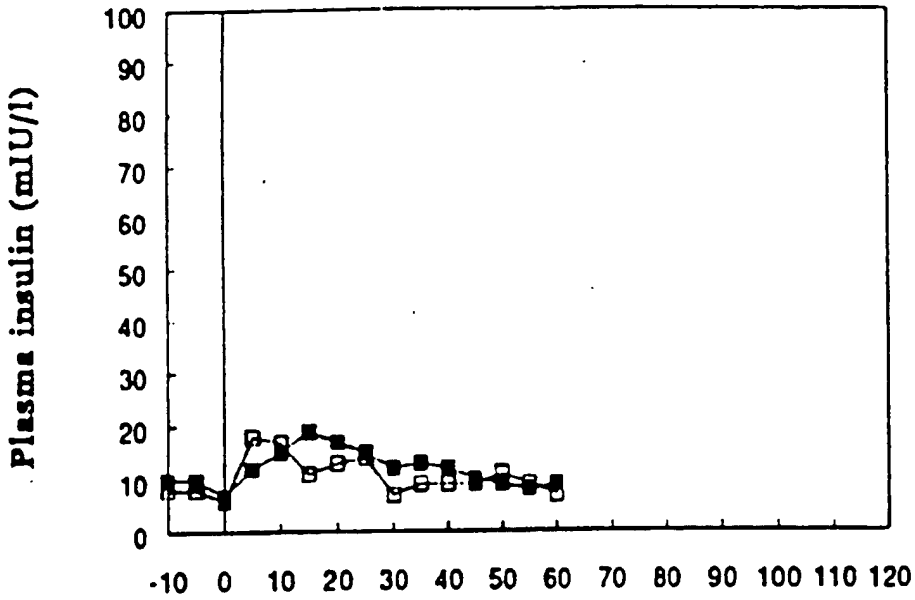

Figure 1 A

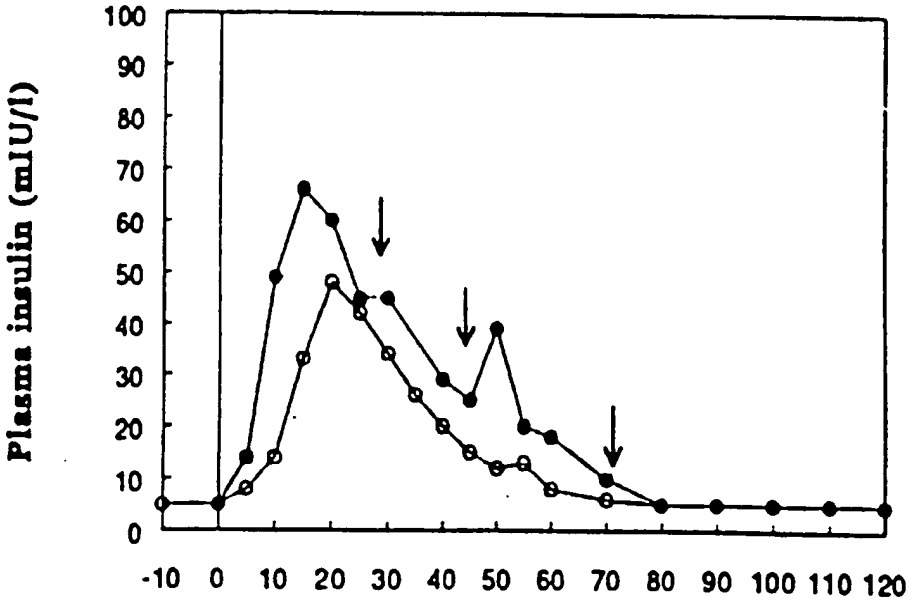

Figure 2 A

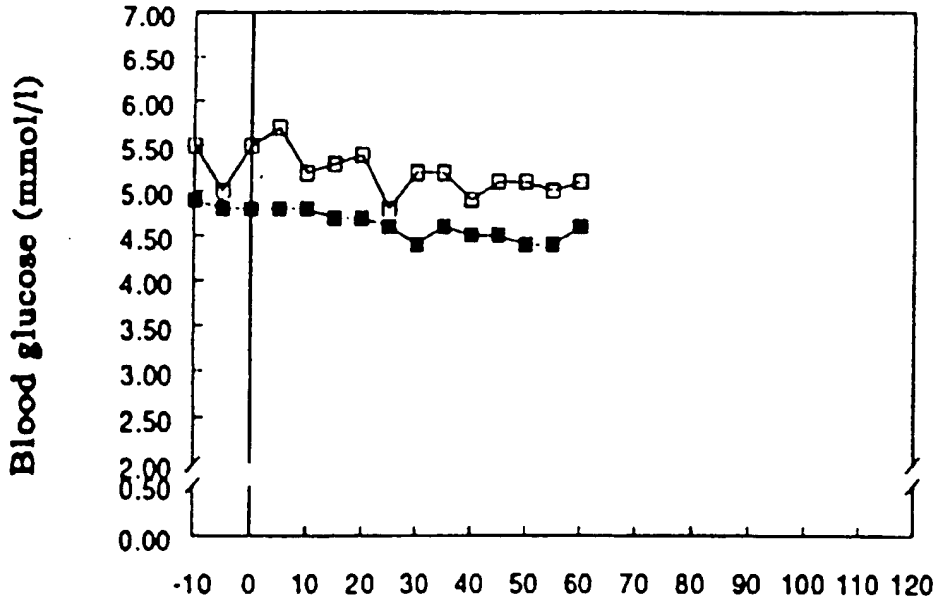

Figure 1B

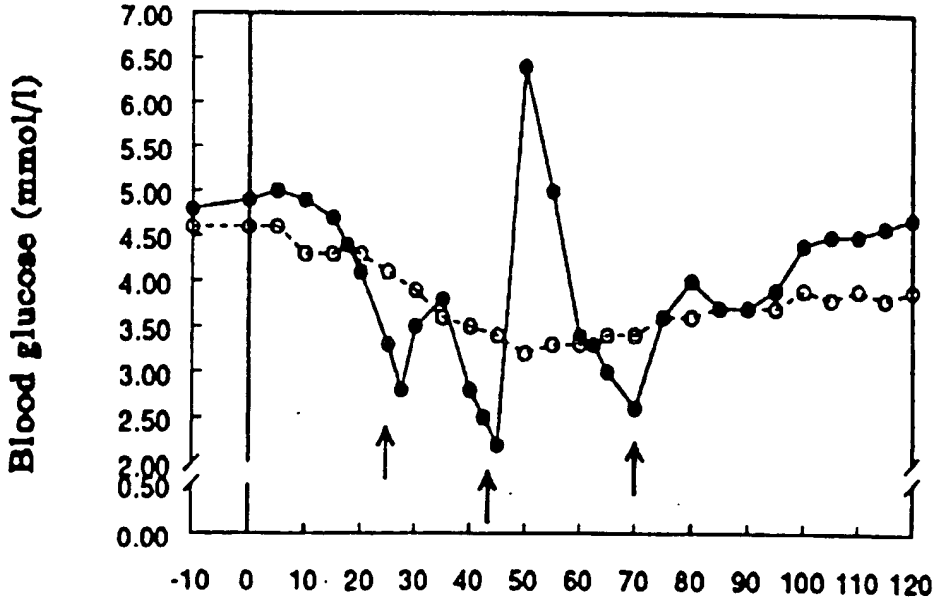

Figure 2B

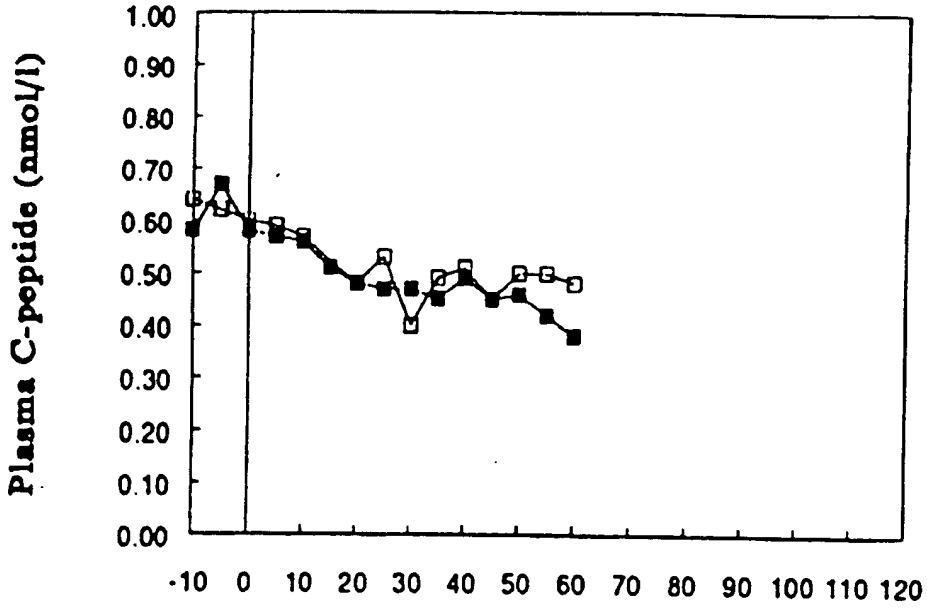

Figure 1C

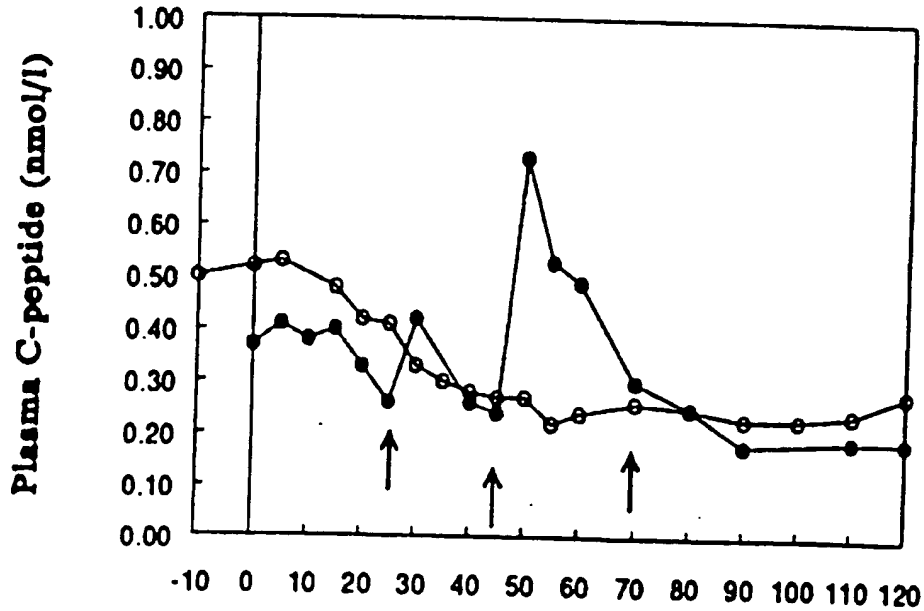

Figure 2C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 94/00892

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K37/02 A61K9/00 A61K47/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 094 157 (TAKEDA) 16 November 1983 see claims 1,2,4,8 see page 5, line 16 see page 6, line 29 see page 7, line 9 see page 7, line 36 see page 10, line 1 - line 17 --- -/--	1,3,5,8, 9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 June 1994	01. 07. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Scarponi, U

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 94/00892

C.(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 117, no. 18, 2 November 1992, Columbus, Ohio, US; abstract no. 178241b, see abstract & PHARM.RES. vol. 9, no. 9 , 1992 pages 1157 - 1163 Z.SHAO ET AL. 'CYCLODEXTRINS AS NASAL ABSORPTION PROMOTERS OF INSULIN:MECHANISTIC EVALUATIONS' ---	1-3,9
X	WO,A,92 01440 (RIJKSUNIVERSITEIT TE LEIDEN,NL) 6 February 1992 cited in the application see claims 1-3,5-8,10 see example 1 ---	1-3,9
Y	EP,A,0 308 181 (NOVO INDUSTRI A/S) 22 March 1989 cited in the application see claims 1,5,7-9 see column 3, line 54 - line 57 see column 4, line 23 see column 4, line 58 see column 6, line 1 see column 6, line 13 ---	1-9
Y	WO,A,92 16196 (NOVO NORDISK A/S) 1 October 1992 cited in the application see claims 1,5,7,8 see page 5, line 4 - line 6 see page 7, line 24 see page 8, line 11 - line 12 ---	1-9
A	DATABASE WPI Week 8925, Derwent Publications Ltd., London, GB; AN 89-181251 (25) see abstract & JP,A,1 117 825 (SANWA KAGAKU KENKYUSHO) 10 May 1989 ---	1-9
A	DATABASE WPI Week 9120, Derwent Publications Ltd., London, GB; AN 91-146147 (20) see abstract & JP,A,3 083 915 (WAKO PURE CHEM. IND.KK) 9 April 1991 -----	1-9

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claim 9 is directed to a method of treatment of the human body by therapy (Rule 39.1(IV)PCT), the search has been carried out and based upon the alleged effects of the compositions.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/EP 94/00892

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